

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Larsen et al.	Confirmation No.:	5189
Serial No.:	10/534,201	Art Unit:	1654
§ 371(c) Date:	April 7, 2006	Examiner:	Maury A. Audet
Customer No.:	21559		
Title:	PEPTIDE GAP JUNCTION MODULATORS		

PETITION UNDER 37 C.F.R. § 1.181 TO WITHDRAW FINALITY

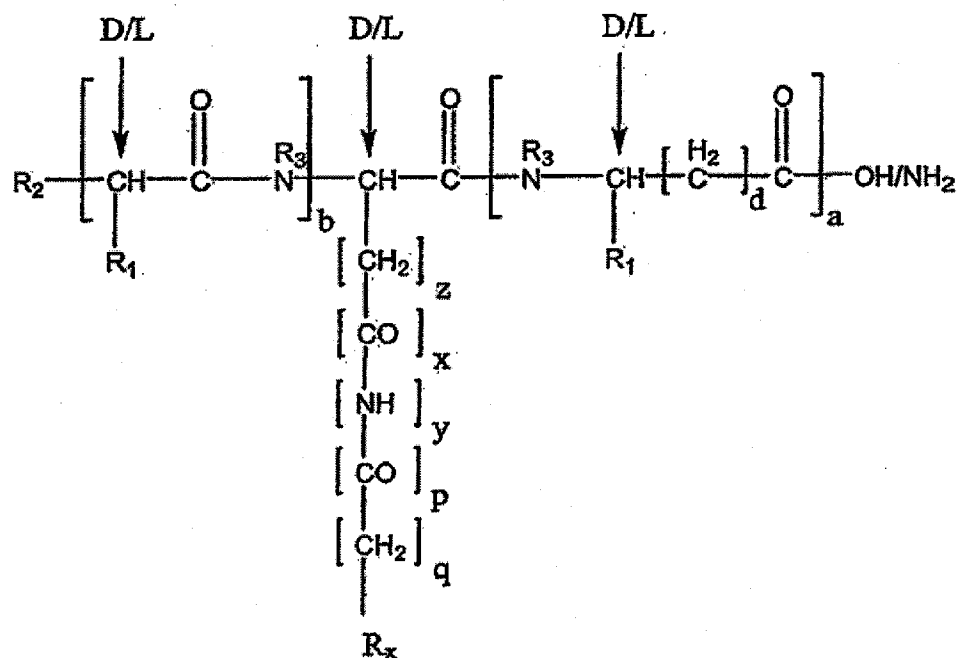
Applicants hereby petition under 37 C.F.R. § 1.181 that the finality of the rejection of claims 1, 56, 57, 61-73, 75-80, 83, and 84 in the final Office action dated March 17, 2011 ("the March 17<sup>th</sup> action") be withdrawn.

*Statement of the facts*

Applicants have developed peptides that are made up of two amino acids (dipeptides), particularly Lys-Gly and Gly-Lys compounds, where the Lys side chain has been modified by addition of a hydrophobic side chain.

Independent claim 1 and exemplary dependent claim 80, as pending prior to previous, non-final action that was mailed January 27, 2009 ("the January 27<sup>th</sup> action"), is reproduced below.

1. A peptide represented by the general formula I:



or a pharmaceutically acceptable salt thereof,

wherein, if a is 1 then b is 0;

if a is 0 then b is 1;

z is 4;

p is 1, x and q are 0, and y is 1;

d is 0;

wherein R<sub>1</sub> is the amino acid side chain of glycine;

wherein R<sub>2</sub> is selected from the group consisting of NH<sub>2</sub>, NHR, NR<sub>2</sub>, NR<sub>3</sub><sup>+</sup>H, OH, SH, RO, RS, RSO, RSO<sub>2</sub>, COR, CSR, COOH, COOR, CONH<sub>2</sub>, CONHR, CONR<sub>2</sub>, OCOR, and SCOR, wherein R is alkyl, alkenyl, aryl, aralkyl, or cycloalkyl;

wherein R<sub>3</sub> is H or CH<sub>3</sub>; and

wherein R<sub>x</sub> is a hydrophobic group.

80. The peptide of claim 79, or a pharmaceutically acceptable salt thereof, wherein said peptide is H-D-Lys(4-t-butylbenzoyl)-Gly-OH (Compound 54).

Claim 1 thus encompasses a genus of Lys-Gly and Gly-Lys peptides with modifications of the Lys side chain. Claim 80 depends from claim 79, which recites a group of dipeptides that includes Compound 54. Claim 79, in turn, depends from claim 1. Claim 80 thus encompasses a particular Lys-Gly compound, or pharmaceutically acceptable salt of that compound.

In the January 27<sup>th</sup> action, claims 1 and 80 were rejected as being obvious over U.S. Patent No. 6, 395,532.

In their reply dated July 14, 2009, Applicants made no amendments to either claim 1 or 80. The Office then issued a "Miscellaneous Action" on November 13, 2009 in which the Office asserted that "metes and bounds of the claimed invention of formula I...are confusingly claimed," pointing out that certain claim elements, such as x, q, and d, which are recited in the structure, are absent from the claimed subject matter. The Office also requested that the genus presented above, which encompasses both Lys-Gly and Gly-Lys peptides, be rewritten as two subgenuses. The Office concludes by stating:

This will ensure that the metes and bounds of the 2 subgenus [*sic*] are distinctly claimed and remove issues of variable scenarios. And that the updated search of the art is properly applied against the 2 respectively subgenus structures of the claimed invention.

This request is being made in order to distinctly claim the invention, commensurate in scope with the actual elements that are to be present in the claimed invention.

Applicants, in their December 14, 2009 ("the December 14<sup>th</sup> response), attempted to comply with this request. Claim 1 was amended to recite two structures instead of one. Elements that were recited in the previous structure but indicated as absent (i.e., elements x, q, and d) were deleted from the new structures. Elements a and b were also deleted because reference to these elements was rendered unnecessary by representing the claimed compounds as two separate structures. Element z was removed and replaced in the structure with the number 4, and each R<sub>1</sub> group, which was limited to the "the amino

acid side chain of glycine” in the previous structure was replaced with a hydrogen (H). Claim 80 was not amended in the December 14<sup>th</sup> response. The amendments to claim 1 were not intended to alter claim scope.

Following these amendments, the Office issued a second “Miscellaneous Action” on April 1, 2010 (“the April 1<sup>st</sup> action”), stating:

[T]he amended claims are unsearchable. The 4th bond of one of the carbonyl groups in each of the 2 subgenuses now claimed in empty. The claims are indefinite as to what molecule is to be attached here. Leaving all the species claimed in dependent claims arguably now lacking [*sic*] antecedent basis.

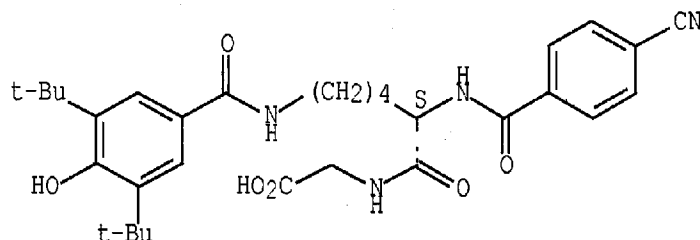
As explained in the April 1<sup>st</sup> action, Applicant also agreed to amend the term “hydrophobic group” to what is described in the specification.

Applicants responded on May 3, 2010 (“the May 3<sup>rd</sup> response”) to address the issue raised by the Office. The structure recited in claim 1, prior to the December 14<sup>th</sup> response, did not include representation of hydrogen atoms. In the December 14<sup>th</sup> response, Applicants amended claim 1 to recite the side chain of glycine (a hydrogen atom) in the structure as an “H” rather than as “R<sub>1</sub>.” Thus, to maintain consistency, Applicants introduced hydrogen (H) moieties at the appropriate positions into the structures of claim 1 in their May 3<sup>rd</sup> response.

Applicants also amended claim 1 to recite that the R<sub>x</sub> moiety is “an optionally substituted aromatic carbon ring” rather than “a hydrophobic group.” This change was made at the request of the Office and incorporates the definition of “hydrophobic group” recited in the specification (page 51, lines 18-19). Again, claim 80 was not amended in the May 3<sup>rd</sup> response, and the claim amendments to claim 1 were not intended to alter claim scope.

The Examiner then issued a Restriction Requirement on July 22, 2010, requiring that Applicants elect one of the two subgenuses now recited in claim 1 for examination. Applicants responded to the Restriction requirement on December 22, 2010, traversing the Restriction Requirement and electing Lys-Gly compounds for examination. The Office then issued a final rejection dated March 17, 2011, in which the

Restriction Requirement was held in abeyance and all claims, including claims 1 and 80, were newly rejected as being either anticipated or obvious over Rahman et al., J Org Chem 63:6196-99, 1998 ("Rahman"), which is cited as teaching the following compound:



The Office set forth the new rejection on the following grounds:

If not expressly teaching the variable genus modified sidechain of the presently claimed Gly-Lys dipeptides, it would have been obvious to one of ordinary skill in the art at the time the invention was made to synthesize Lys-Gly dipeptides, bearing any type of known side chain modifications well known in the peptides arts...because Rahman et al. advantageously teaches the Lys-Gly dipeptide above with modified sidechain [*sic*]. Absent evidence to the contrary of some unexpected result (e.g. in treating arrhythmias), using one side chain alternative versus others [*sic*].

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

The Office made this action final on the grounds that Applicants' amendment necessitated the new ground for rejection.

Because this rejection could have been brought prior to Applicants' amendments in the December 14<sup>th</sup> and May 3<sup>rd</sup> responses, withdrawal of finality is requested.

*Requirement for making an Office action final*

The M.P.E.P. sets forth the criteria for making a rejection final.

Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims, nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p).

MPEP § 706.07(a). Because this rejection was not based on information submitted on an information disclosure statement (IDS), Applicants address the issue of whether any of the amendments made subsequent to the January 27<sup>th</sup> action necessitated the new ground for rejection set forth in the March 17<sup>th</sup> action.

*Analysis*

In determining if a claim amendment "necessitates a new ground of rejection," the critical issue is whether that ground for rejection could have been made prior to the amendment or amendments being entered. To make this determination, both the claim, prior to the amendment(s) in question, and the reasoning behind the new rejection must be carefully examined. It is then necessary to ask whether the reasoning behind this new rejection can be applied to the unamended claim. If a rejection based on this same reasoning could have been applied to the unamended claim, it is clear that the amendment did not necessitate the new ground for rejection. Here, the new rejection set forth in the March 17<sup>th</sup> action could have been made against the claims prior to the amendments in the May 3<sup>rd</sup> and December 14<sup>th</sup> responses. Thus, Applicants' amendments did not necessitate the new ground for rejection. Making the March 17<sup>th</sup> action final is therefore improper. Applicants' analysis is presented below.

### *Claim 80*

Applicants first address the new rejection as applied to claim 80. Claim 80 recites:  
80. The peptide of claim 79, or a pharmaceutically acceptable salt thereof, wherein said peptide is H-D-Lys(4-t-butylbenzoyl)-Gly-OH (Compound 54).

Claim 80 is thus directed to a single compound (Compound 54) or a pharmaceutically acceptable salt of that compound. This claim was not amended in either the December 14<sup>th</sup> or the May 3<sup>rd</sup> responses.

As explained above, a new rejection may be brought in a final action only where that rejection is necessitated by Applicants' amendment. The question is therefore whether the amendments to claim 1 necessitated the new rejection of claim 80 as being anticipated by, or obvious over, Rahman. Applicants respectfully submit that these amendments did not.

As explained above, the Office takes the position that Rahman either teaches the claimed compounds or that it would be obvious to make the claimed compounds based on the compound disclosed in Rahman. Because the compound recited in claim 80 has a structure different from the compound of Rahman, the Office must be setting forth this rejection on an obviousness basis, taking the position that the compound of claim 80 is structurally obvious over the compound of Rahman.

The amendments to claim 1 in the December 14<sup>th</sup> and May 3<sup>rd</sup> replies did not change the structure of the compound of claim 80 and therefore did not change the scope of this claim. Accordingly, a rejection over Rahman, based on the same reasoning as the new rejection set forth in the March 17<sup>th</sup> action, could have been made prior the Applicants' amendments. These amendments therefore did not necessitate the new ground for rejection. For this reason, making the March 17<sup>th</sup> action final is improper. Withdrawal of finality is accordingly requested.

### *Claim 1*

Applicants' amendments to claim 1 also did not necessitate the new rejection set forth in the March 17<sup>th</sup> action. As explained in detail above, the amendments to claim 1

in the December 14<sup>th</sup> and May 3<sup>rd</sup> responses split the genus structure into two substructures, removed structural elements that were indicated as being absent, and replaced the term “hydrophobic group” with its definition in the specification, i.e., an “an optionally substituted aromatic carbon ring.”

These amendments did not broaden claim 1. As explained above, the question is whether the claim, prior to amendment, could have been rejected on the same grounds set forth in the new rejection. Because amended claim 1 is not broader in scope than unamended claim 1, unamended claim 1 encompasses the subject matter of amended claim 1. Thus, if amended claim 1 was either anticipated by or obvious over the compound of Rahman, it necessarily follows that a claim of the same or broader scope, such as unamended claim 1, would also have been either anticipated or obvious over the same reference. For this reason, the new rejection in the March 17<sup>th</sup> action could have been brought against claim 1 prior to Applicants’ amendments. Applicants’ amendments therefore cannot have necessitated the new rejection. For this reason as well, withdrawal of finality of the March 17<sup>th</sup> action is respectfully requested.

*The Office must do more than simply assert that the amendments necessitated the new rejection*

For the Office to make its case, it not enough to simply assert that Applicants’ amendment “necessitated” the new rejection. It must show, under the analytical framework outlined above, that the new rejection could not have been applied to unamended claim 1 or 80. On this point, the Office has failed to provide any line of reasoning to support such a conclusion. Thus, there is no basis for concluding that finality is proper.

*An amendment or a new search, by itself, does not indicate that the amendments necessitated the new rejection*

Applicants do not dispute that amendments were made to claim 1 nor do Applicants dispute that the Office conducted a new search of the claimed subject matter



following these amendments. However, neither of these facts alone provides a sufficient basis for concluding that Applicants' amendment necessitated the new rejection. This determination can only be made by comparing the new rejection to each claim prior to amendment, and asking whether that same rejection could have been brought against the unamended claim. As explained above, both claim 1 and claim 80 could have been rejected as being anticipated by or obvious over Rahman prior to Applicants' amendments based upon the same rationale set forth in the March 17<sup>th</sup> action. Thus, these amendments did not necessitate the Office's new rejection. Under these circumstances, finality is improper and should be withdrawn.

*All amendments were made solely at the Examiner's request and not in response to rejections of record*

Finally, Applicants note that the amendments made in both the December 14<sup>th</sup> and the May 3<sup>rd</sup> replies were done solely at the request of the Examiner in order to aid in searching the claimed structure. These amendments were not made either to alter the scope of the claims or in response to a rejection. In this situation, it is entirely unfair for the Office to bring a new rejection that could have been presented earlier and argue that Applicants' amendments somehow necessitated this rejection.

Indeed, doing so deprives Applicants of their fair opportunity to address any and all rejections raised by the Office. Here, the Office failed to bring a particular rejection in the first action and then subsequently brought that rejection in a second action that is made final, following claim amendments that were made at the Examiner's request. The M.P.E.P. makes it clear that the Office can make a rejection final only if an Applicants' amendment or information in an IDS forced the Office to issue a new rejection that it otherwise could not have brought. This is not the case here. By making the March 17<sup>th</sup> action final, the Office is depriving Applicants' their fair opportunity to address the rejection over Rahman, a rejection that could have been made prior to the amendments in the December 14<sup>th</sup> and May 3<sup>rd</sup> responses.

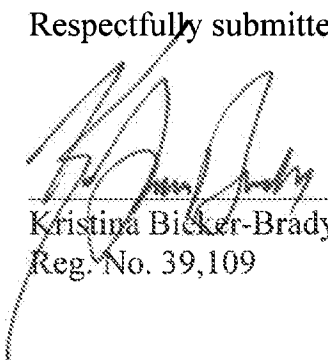
CONCLUSION

Applicants respectfully submit that the Office has failed to demonstrate that Applicants' amendments necessitated the rejection over Rahman set forth in the March 17<sup>th</sup> action. Withdrawal of finality of the March 17<sup>th</sup> action is therefore respectfully requested.

No fees are believed to be due at this time. However, if there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: May 13, 2011

  
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Kristina Bicker-Brady, Ph.D.  
Reg. No. 39,109

Clark & Elbing LLP  
101 Federal Street  
Boston, MA 02110  
Telephone: 617-428-0200  
Facsimile: 617-428-7045